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Reagent Marketing Compliance: Controlling Your Intended Use

Agenda

1. Intended Use
2. The Regulatory Categories
3. FDA Regulatory And Enforcement Activity
4. Controlling Your Intended Use

Warning: *this presentation contains concepts engineers will find fuzzy and illogical, which may lead to anxiety and nausea. Please consult your attorney if you feel the need to throw anything in frustration.*

One Theme Today

- How to avoid promoting beyond the lawful label
  - RUO/IUO Category
  - ASR
  - IVD

Intended Use

- Each category has limited, permitted intended uses
  - RUO, only for “research”
  - IUO, only for “investigation”
  - ASR, only as building blocks for houses designed by the customer
  - IVD, only for what FDA clears or approves

Basic Intended Use Legal Standard

Under 21 CFR 801.4,

1. [T]he words “intended uses” … refer to the objective intent of the persons legally responsible for the labeling of devices.
2. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article.
3. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.
4. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised.

An Important Intuitive Point

FDA will view with great angst any manufacturer's program that appears designed to circumvent ***the agency's fundamental role of reviewing and approving tests for clinical use***

What Does Objective Intent Mean?

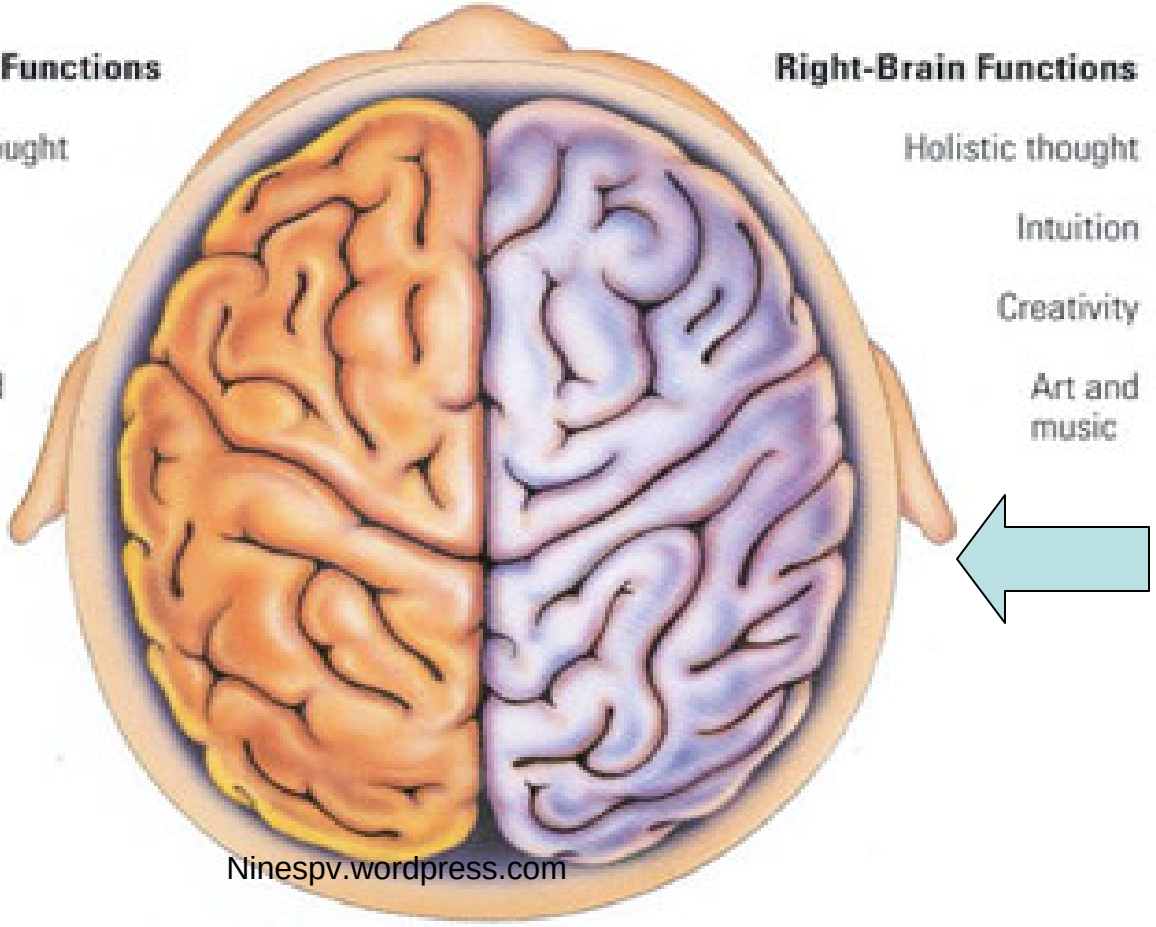
- In a typical criminal case, prosecution shows objective intent of the accused by reference to words, deeds, and knowledge.
  - Don't have a mind probe.
  - Defendant is charged by what a reasonable person would've intended in light of that evidence.
- Defense would try to show subjective intent.
  - Notwithstanding what others might have intended in those circumstances, this particular defendant did not intend that, perhaps because
    - He is incredibly stupid, insane or in some way not a reasonable person.
- In the case of FDA intended use, we only look at objective intent.
  - May mean we will only look at the evidence of intent and
  - Not permit the discussion about whether the manufacturer was somehow stupid, insane or not reasonable.

For The Next Several Slides

EXPERIENCE =

USABILITY/ANALYTIC + DESIGN/CREATIVE

Left-Brain Functions	Right-Brain Functions
Analytic thought	Holistic thought
Logic	Intuition
Language	Creativity
Science and math	Art and music



Ninespv.wordpress.com

Use this side

Determining the Intended Use of a Stick

Statements Suggesting Popsicle Stick	Statements suggesting Pediatric Tongue Depressor
It's a popsicle stick	It's a Pediatric Tongue Depressor
Sterilized to food grade	Sterilized to medical grade
Kids love it	Young patients love it
Makes popsicles last longer	Narrow enough to access those hard to reach places in a kid's mouth
← Tastes	Great →

Promoting Beyond the Label: The Elements vs. The Evidence

The Elements

- Placing a device into interstate commerce
- Making claims that go beyond the lawful label
  - Express claims
  - Implied claims

The Evidence

- Presence in interstate commerce
- Evidence of intent to make a claim
  - Words
  - Deeds
  - Knowledge of circumstances

Express Claims Beyond the Label

Prohibited

- Labeling
  - Brochures
  - Reprints handed to customers
- Advertising
- Oral Sales pitches
- Presentations
- Tainted CME
- Promotional websites, and potentially social media
- Other promotional avenues

Allowed

- Information sharing, not really claims
- Certain legitimate forums for:
  - Scientific discussions
  - Investor updates
  - Payor discussions
  - Unsolicited questions

Nature of Express Claims that Cross the Line

- Promote an off label use by suggesting such use is:
  - safe,
  - effective,
  - wise,
  - common,
  - possible,
  - Just about anything else that is not negative

Anatomy of an Implied Claim

- Screws Unlimited, Ltd. simply sells screws
- No words to describe the product other than
  - A screw
  - Flank Overlap Area (FOA; 261 mm2) results from narrowing the conical core in the thread area
  - Made of Titanium
  - Sterile
  - $100 price per screw
  - Offered through a distributor that serves hospitals
  - The label says “For research use only”

The Case of the Loose Screw

- The government investigates and finds:
  - All of the customers are using the screws as pedicle screws in patients
    - No evidence that anyone is interested in them for research
  - The thread design corresponds to a well-known clinical trial that showed that particular design to be the best for pedicle screw spinal fixation
  - The internal business plan and email make clear that the company expected all of the sales to be for pedicle fixation in patients
- Does the government have a case?

Analyzing an Implied Claim

Threshold is when the implied claim
could reasonably start to influence buyers

Self Evident

Barely Perceptible

Three tests for determining the existence of an implied claim

1. How the agency interprets the claims made
    a) Reviewable by the courts
2. How the customers interpret the claims made
    a) Evidence of actual use
3. What the internal evidence of manufacturer intent says about the purpose of the claims

Intended Use: Judging the Evidence

Words

- Labeling, sales lit. advertising, sales pitches
- Business planning
- Internal memos, training
- Verbal Statements

Actions

- Design features (i.e. uniquely clinical features)
- Where do your sales people visit (shows and customers)?
- Who are you talking to?

Circumstances

- How valid are non medical uses
- Has FDA rejected the use?
- Sales volume related to medical use
- Proportion of sales rev from unapproved indications

Gestalt Theory

The totality determines the outcome

Few bright lines for any one factor.
Need to weigh all of the evidence.

What the Test is Not

- Buyer's intent: the seller controls his fate
- Foreseeable use
  - It is foreseeable that customers will use the product in lots of different ways, some of them downright stupid
  - Foreseeable test ignores the ability of the manufacturer to reinforce its intent through controls
- Actual Use
  - Only when it becomes so predominant that it is fair to impute the intent to the manufacturer

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RUOs

- So what the heck is “research”?
  - Let’s look at three buckets of uses
  - Common element is the results are not reported to a patient or his caregiver

1. Unregulated Research Activities

- Basic, unapplied research to answer questions about how, for example, cells, tissue or organs respond to an intervention
  - The goal has to be some fundamental scientific knowledge, not helping a subject or patient
- Applied research where the questions relate to how, for example, cells, tissue or organs respond in the context of the development of a therapy
  - Permitted. Data/results only used to guide the research on the therapy
  - Not permitted. No communication to a subject/patient or his caregivers

2. FDA Regulation of Therapeutics

- Sales to drug or biological product companies
  - Start to enter FDA jurisdiction indirectly under Good Laboratory Practices when the testing will be used as a basis for FDA decision-making on whether to allow clinical testing for a therapeutic product
    - If the study includes gathering any information on the performance of the reagent/instrument, the study becomes investigational for the diagnostic
  - Potentially a GMP or approval issue for the therapeutic product being made, if the instrument or reagent is used to make the therapeutic product

3. FDA Regulated Research Using RUOs

- Research to assess the potential usefulness of the reagent/instrument for a clinical diagnostic
  - Can use animal or human specimens
  - Results cannot be shared with the subject/patient or his caregivers
  - Results can only be used to guide the research on the usefulness of the reagent/instrument

Research Products are Not RUOs!

- RUOs involve research ***on*** the reagent,
  - i.e. where the protocol is designed to produce information about the characteristics of the reagent.
- Research products involve research ***using*** the reagent,
  - i.e. where the protocol is designed to produce information on something else.
- Labeling a research product as “RUO” causes confusion, and can lead FDA to one day expect the company to seek clearance

IUOs

- IUOs, in contrast to RUOs, contemplate that information will be shared with a patient or his caregiver.
- Can involve an IDE or fall within the exemption.
- Can collect data or sell to investigator initiated trials

ASRs

- What are the primary marketing limitations for ASRs?
  - Consider classification
  - Consider restricted device status

ASR Classification

ASRs may be in class I, II or III, with attendant premarket requirements

- Class I are exempt from 510(k)
- An ASR is a Class II device if the reagent is used as a component in a blood banking test of a type that has been classified as a Class II. 21 CFR 864.4020(b)(2).

ASR Classification

- An ASR is a Class III device if the reagent is intended as a component in tests intended either:
  - to diagnose a contagious condition that is highly likely to result in a fatal outcome and prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition (e.g., HIV/AIDS or TB); or
  - for use in donor screening for conditions for which FDA has recommended or required testing in order to safeguard the blood supply or establish the safe use of blood and blood products (e.g., tests for hepatitis or for identifying blood groups). 21 CFR 864.4020(b)(3) or
  - to be used as a component in tests for diagnosis of HIV (including monitoring for viral load or HIV drug resistance mutations)

ASR Requirements

- Clarified in 2007 Guidance
- ASRs are subject to :
  - Special restrictions on the sale and promotion, such as only to *high complexity labs* and limited instructions for use; and
  - *Disclosures to end users* that analytical and performance characteristics are not established.

ASR Manufacturer Marketing Practices

Overview

- Singularity.
  - Used to detect a single ligand or target (e.g., protein, single nucleotide change, epitope);
  - Because ASRs are building blocks of LDTs, they cannot be promoted or sold together with other ASRs or general purpose reagents (GPRs).
- No specific purposes. Manufacturers must avoid marketing ASRs in a manner that suggests use of particular ASRs together for a specific purpose.
- No IFUs. Manufacturers *cannot* provide instructions (or application sheets) for developing or performing an assay with an ASR.
  - The IFU should include only information for proper storage, handling, chemical composition, concentration, cross-reactivities, stability, etc.
- No Claims.
  - ASR manufacturers should not make claims to laboratories regarding analytical or clinical performance for ASRs.

ASR Manufacturer Marketing Practices

Communication/help

- Counseling. Labs are responsible for the design and performance of the test. The manufacturer cannot tell a lab which ASRs are useful for a particular application.
- Validation. An ASR manufacturer should not assist with the development or validation of an LDT using its specific ASR.
- Literature. Manufacturers can provide labs with peer-reviewed / published literature on the characteristics of the ASR itself (single target).
  - However, may not send articles/info that describes the use of an ASR in a specific test or application, or information regarding an ASR's clinical utility, clinical performance, or validation protocols.

RUO vs ASR

Restrictions	RUO	ASR
Can they be intended for clinical use?	No	Yes
Do they need to be singular?	No	Yes
Are they subject to GMPs, registration and listing?	No	Yes
Can they be sold as kits?	Yes	No
Can instructions for use be provided?	Yes, limited	No
Can labeling include clinical discussion?	No	No
Can labeling include performance claims—analytical or clinical?	Some analytical	No
Do they require a customer certification program?	Yes	No

IVDs

- Have a cleared or approved intended use
- Must promote within that intended use

A Framework for Segmenting Research and Investigation

	Research ***using*** the Reagent But ***Not*** Producing Results that Can Affect a Patient				Research ***on*** the Reagent		Use in Clinical Trials for Another Therapy
Institution	Basic research not using human cells	Basic human cellular, tissue or organ research.	Therapeutic product discovery: used in a test on human tissue, results ***not*** affect a subject/patient	Therapeutic procedure discovery: used in a test on human tissue, results ***not*** affect a subject/patient	Looking for possible clinical applications	Evaluating clinical applications through investigation	Use for clinical testing; results reported to patient
Hospitals doing research	Research product	Research product	Research product	Research product	RUO	IUO/IDE	IVD/ASR
Pharma and cell therapy companies/central lab	Research product	Research product	Therapeutic regulators and possibly investigational requirements		RUO	IUO/IDE	IVD/ASR
Clinical laboratories that also do research (high complexity)	Research product	Research product	Research product	Research product	RUO	IUO/IDE	IVD/ASR
Clinical laboratories that do not do much research (moderate complexity or waived)	Companies need to be particularly vigilant if they plan to sell research type products to an institution that does not ordinarily do research.					IUO/IDE	IVD/ASR

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1991-92

A 1991 letter from FDA to industry described the industry's obligations to limit distribution of RUO products:

"There must be predetermined limits on the number of independent … researchers, and the number of patients or patient samples utilized by each … researcher, and on the time periods for the studies. Product distribution must be discontinued at the completion of each study."

In 1992, FDA proposed a so-called accommodation list—that included many Flow Cy products—to allow manufacturers to stay on the market while they pursued approval.

1998

- FDA reiterated its understanding that,
  - "Many manufacturers of IVDs have not followed the requirements…. As a result, numerous IVDs labeled for research … purposes are being promoted, distributed, and used for purposes other than research…. This commercialization has resulted in widespread use of laboratory tests with unproven performance characteristics. Use of such tests may mislead providers of medical diagnosis and treatment and cause serious adverse health consequences to unknowing patients." [emphasis added]

Still 1998

- But FDA was still on the horns of a dilemma. They recognized that many of these reagents had become part of the standard of care. The agency explained:
  - "The agency recognizes that certain improperly commercialized IVDs have been in extensive clinical use for a significant period of time. The agency further recognizes that immediate regulatory action against certain of these IVDs might result in adverse consequences to individual patients and the public health. Therefore, FDA is publishing this CPG in order to describe the agency's enforcement policy, which includes the agency's intention to exercise discretion for designated periods of time, so as not to cause undue disruption to the possibly beneficial use of IVDs that have not received agency clearance prior to commercialization."
- The agency gave several criteria it would use to decide how long it would wait before proceeding with an enforcement action. The waiting period was intended to allow manufacturers to seek clearance.

More 1998

- The agency further outlined its expectations with regard to how RUOs would be promoted and the structure of a certification program
  - "Expected values (reference values) and specific performance characteristics described at 21 CFR 809.10(b)(11) and (12) should not be included in the labeling because one of the purposes of the research is to study and establish the subject IVDs performance parameters for its intended use."
  - "FDA strongly encourages manufacturers… of 'research use' in vitro products to maintain a certification program that documents the researcher's agreement that the device will not be used for investigations involving clinical use including diagnosis, prognosis and monitoring of a disease state and will not be used in conjunction with patient records or treatment."
- The CPG was never finalized reportedly because of legal concerns regarding the need for rulemaking.

2007

- FDA issues Final ASR guidance
  - Warns against using RUO as a replacement regulatory category
  - Gives one year amnesty for companies to come into compliance
  - Big shift in industry

2010

- FDA
  - Fires shots across industry's bow
  - Goes on speaking campaign to put industry on notice
    - Next slide is by Liz Mansfield in 2010
  - Promises new guidance on RUOs soon

RUO Inappropriate Marketing

- Labeling
  - Includes intended use
    - See 21 CFR 801.4 on intent
  - Includes clinical information
  - Includes clinical interpretation guidelines
  - References diagnostic use
- Sold for clinical use

Warning Letters and other Enforcement

- Off-Label Marketing of Research Use Only products
  - BioCheck, Inc. (Warning Letter December 10, 2010)
    - FDA inspection indicated that the company manufactured and distributed one product labeled for Research Use Only (“RUO”) and three products labeled for Investigational Use Only (“IUO”) for which product inserts included intended use statements, test, preparation, and calculation methods, therefore making these products devices as opposed to Research or Investigational products.
    - FDA requested BioCheck cease marketing, promoting and distributing these products.
  - American Bio Medica Corporation (Warning Letter July 30, 2009)
    - Based on a review of the Company’s website FDA concluded that the Company was marketing an OTC test system for drugs-of-abuse without FDA marketing clearance of approval.
    - The Company claimed that the products were labeled as “For Forensic Use Only.” However, the Company issued press releases indicating that employers were using these products for post-accident and random drug testing of employees.
    - Based this evidence FDA concluded that the Company was marketing these products for the public use of workplace drug testing.
- Numerous warning letters for off label and unapproved product

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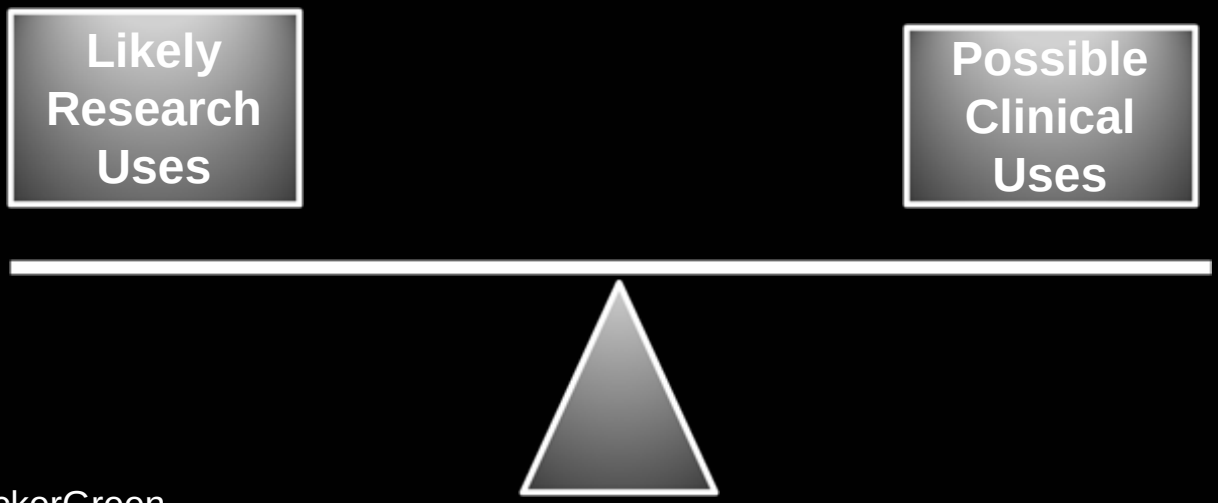
Ensuring Appropriate Intended Use for an RUO

- Do there exist legitimate research uses?
- Are Customers likely to misuse for clinical purposes?

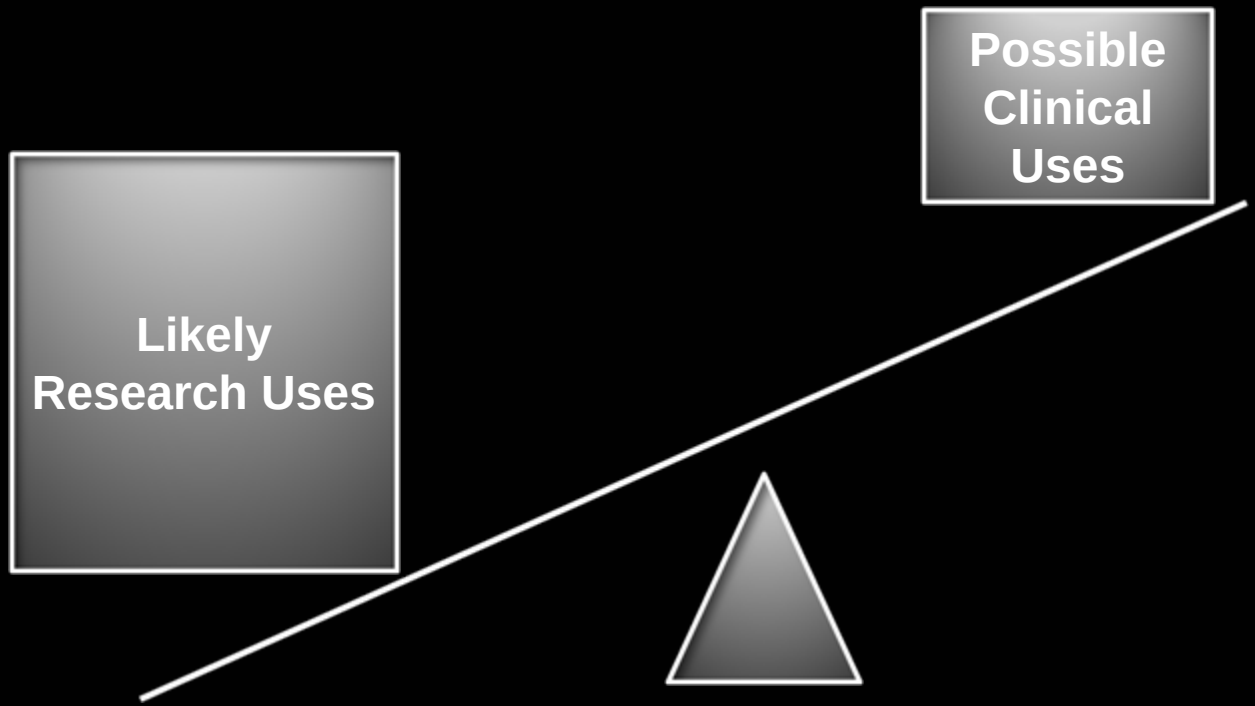


Ensuring Appropriate Intended Use for an RUO

- Design some marketing controls to reduce the risk of medical device use, and to encourage research use
- Revisit this periodically as the facts change, and also to assess the effectiveness of the controls

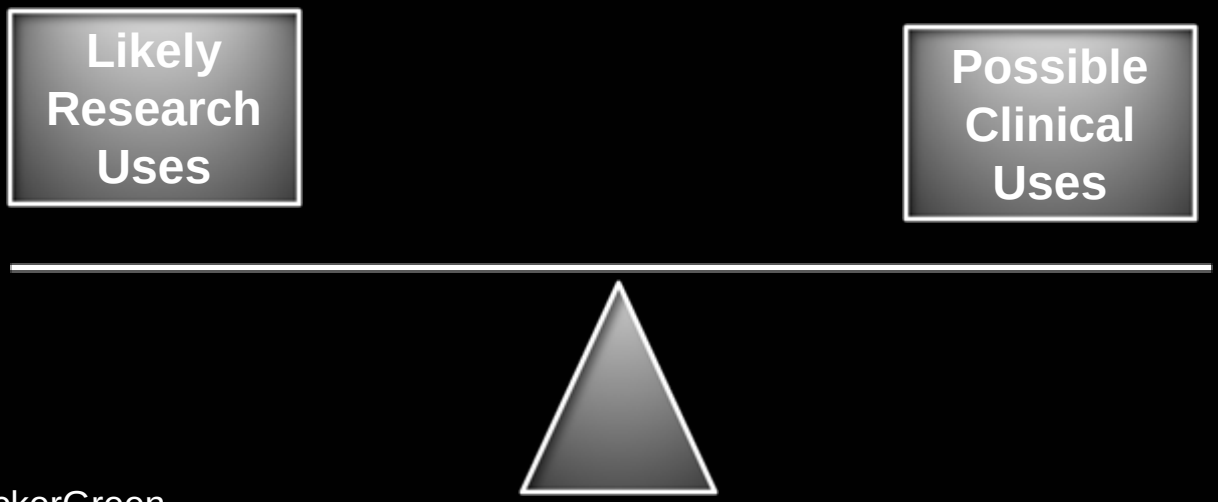
Ensuring Appropriate Intended Use for an RUO

- Make sure the company doesn't make express or implied claims beyond the RUO use
- Don't need to do much more



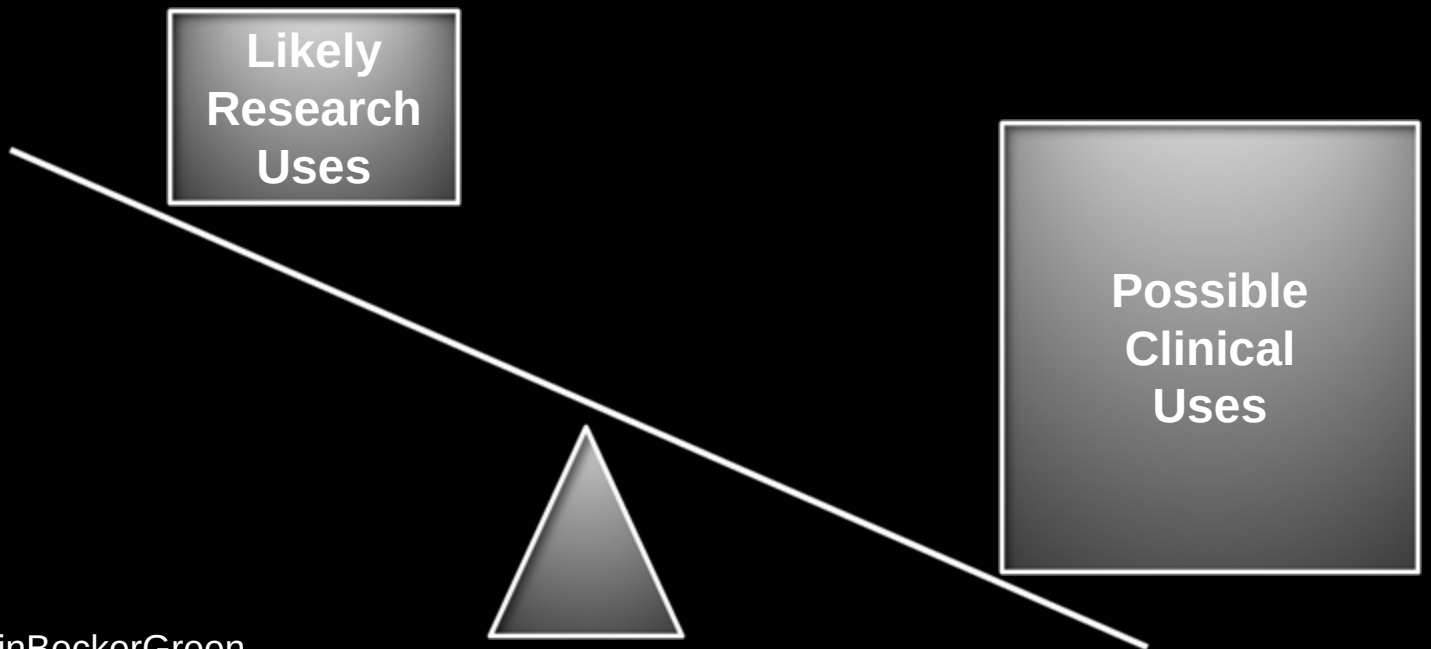
Ensuring Appropriate Intended Use for an RUO

- Make sure the company doesn't make express or implied claims beyond the RUO use
- Add a certification program to (a) ensure customers understand and agree to the limited use, and thereby (b) create evidence of your efforts to properly market



Ensuring Appropriate Intended Use for an RUO

- Make sure the company doesn't make express or implied claims beyond the RUO use
- Perhaps go beyond mere certification to require research protocols and impose quantity limitations



Beyond Selling

- Need to look at how you interact with your customers, to ensure consistency
  - How are you supporting products already sold?
  - Do you continue to sell to customer once you realize they are using it beyond the label?

Some Issues
Not to Worry About

- Off label use from the customer's perspective is legal
- Don't need to investigate specific actual use after the fact
- Off label use does not get the manufacturer in trouble, by itself
- Don't need to report to FDA off label use

Bottom Line

- For all questions about what a company should do in marketing a diagnostic, it is all about:
  - Intent and
  - Evidence of intent though the company's
    - Words
    - Deeds
    - Knowledge
- The gestalt approach: no singular factor and line

Questions?